IN THE CLAIMS:

1-22 (Cancelled)

- 23. (Currently amended) A method of detecting a binding event involving a test protein with a test ligand, the method comprising:
 - (a) providing an unpurified test protein;
 - (b) providing a test ligand;
 - (c) contacting the test ligand with the <u>unpurified</u> test protein to form a test mixture;
 - (d) contacting the test mixture with an exchange buffer comprising a denaturant and deuterium, the exchange buffer having a denaturant concentration;
 - (e) contacting the test mixture with a mass spectrometry matrix medium;
 - (f) determining a change in mass of the test protein by mass spectrometry;
 - (g) varying the denaturant concentration of the exchange buffer;
 - (h) repeating steps (a)-(g) a desired number of times; and
 - (i) analyzing the change in mass of the test protein as a function of denaturant concentration, whereby a binding event involving the test protein and the test ligand is detected.
- 24. (Original) The method of claim 23, wherein the test protein is disposed in a crude cell lysate.
- 25. (Original) The method of claim 23, wherein the test protein is associated with a disease phenotype.
- 26. (Original) The method of claim 23, wherein the disease phenotype is characterized by protein misfolding.
- 27. (Original) The method of claim 23, wherein the test protein has a mass of less than 1,000,000 daltons.

28. (Original) The method of claim 23, wherein the test protein is a multimeric protein.

- 29. (Original) The method of claim 23, wherein the test protein is disposed on a microtiter plate.
- 30. (Original) The method of claim 29, wherein a plurality of test proteins are disposed on the microtiter plate.
- 31. (Original) The method of claim 30, wherein the method further comprises the step of repeating steps (a)-(i) for each test protein disposed on the microtiter plate.
- 32. (Original) The method of claim 23, wherein the test protein is provided in picomolar or greater amounts.
 - 33. (Original) The method of claim 23, wherein the test protein is in vivo.
- 34. (Original) The method of claim 23, wherein the denaturant is a chemical denaturant.
- 35. (Original) The method of claim 34, wherein the denaturant is selected from the group consisting of detergents, guanidinium chloride and urea.
- 36. (Original) The method of claim 23, wherein the mass spectrometry matrix material is a MALDI mass spectrometry matrix material and the mass spectrometry is MALDI mass spectrometry.
- 37. (Original) The method of claim 36, wherein the MALDI mass spectrometry matrix material is selected from the group consisting of sinapinic acid, α -cyano-4-

hydroxycinnamic acid, 2,5-dihdroxybenzoic acid, 2,5-dihydroxyacetophenone and 3-amino-4-hydroxybenzoic acid.

- 38. (Currently amended) The method of claim 23, wherein the analyzing comprises:
 - (a) plotting the change in mass of the test protein in the presence of the test ligand as a function of denaturant concentration to generate a first denaturation curve;
 - (b) plotting the change in mass of the test protein in the absence of the test ligand as a function of denaturant concentration to generate a second denaturation curve; and
 - (c) identifying a change in the position transition midpoint of the first denaturation curve relative to the position transition midpoint of the second denaturation curve, wherein a difference in the positions transition midpoints of the first and second denaturation curves is indicative of a binding event involving the test ligand and the test protein.
- 39. (Original) The method of claim 23, wherein the analyzing is performed using a computer program.
- 40. (Original) The method of claim 23, further comprising providing a reference protein with the test protein.
 - 41-124. (Cancelled).
- 125. (New) A method of detecting a binding event involving a test protein with a test ligand, the method comprising:
 - (a) providing a test protein;
 - (b) providing a test ligand;
 - (c) contacting the test ligand with the test protein to form a test mixture;

- (d) contacting the test mixture with an exchange buffer comprising a denaturant and deuterium for a specified time of exchange (t), the exchange buffer having a denaturant concentration;
- (e) contacting the test mixture with a mass spectrometry matrix medium;
- (f) determining a change in mass of the test protein by mass spectrometry;
- (g) varying the denaturant concentration of the exchange buffer;
- (h) repeating steps (a)-(g) a desired number of times; and
- (i) analyzing the change in mass of the test protein as a function of denaturant concentration and the specified time of exchange (t), whereby a binding event involving the test protein and the test ligand is detected.
- 126. (New) The method of claim 125, wherein the test protein is an unpurified test protein.
- 127. (New) The method of claim 125, wherein the detecting of a binding event further comprises fitting data comprising a change in mass of the test protein as a function of denaturant concentration and the specified time of exchange (t) to the equation $C_{1/2}^{SUPREX} = C_{1/2}^{den}$ (RT/m) $\ln(\langle k_{int} \rangle t/0.693 1)$.